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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,711	BARTEN ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on October 1, 2009 is acknowledged and has been entered. Claims 1-30 are pending. Claims 31-37 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-30 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Previous Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2, 4-9, 12-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280). Wong teaches a method that comprises amplification using tagged primers and hybridization of the amplification products to an identifying tag specific array (Abstract).

With regard to claim 1, Wong teaches a method for detecting different nucleic acids A in parallel, comprising the following steps:

a) providing in each case one first primer which is suitable for carrying out a primer extension together with one of the nucleic acids A and which contains a first primer (P1) and a second primer (P2) (Figure 1, where the format of the primers are disclosed, wherein the primer(s) include a 3' flanking target specific sequence (44), an identifier specific sequence in the middle (42), and a 5' flanking tag sequence (46); see also col. 21, lines 8-28),

with the first primer (P1) exhibiting a 5' terminal first constituent segment (c1) and a 3' terminal second constituent segment (c2) and the second primer (P2) exhibiting a 5' terminal third constituent segment (c3) and a 3' terminal fourth constituent segment (c4), with the sequences of the second constituent segment (c2) and the fourth constituent segment (c4) being selected such that the second constituent segment (c2) can hybridize specifically, under defined first conditions, with a predetermined first segment of the one of the nucleic acids A, and be enzymatically extended, and the fourth constituent segment (c4) can hybridize specifically, under defined second conditions, with a predetermined second segment of a nucleic acid A' which is complementary to the one of the nucleic acids A, and be enzymatically extended (Figure 1, where the format of the primers are disclosed, wherein the primer(s) include a 3'

flanking target specific sequence (44), an identifier specific sequence in the middle (42), and a 5' flanking tag sequence (46); see also col. 21, lines 8-28), and

with in each case an intermediate segment i, which connects the first constituent segment (cl) to the second constituent segment (c2) and is specific for the second constituent segment (c2), or an intermediate segment i, which connects the third constituent segment (c3) to the fourth constituent segment (c4) and is specific for the fourth constituent segment (c4), being provided (col. 4, lines 23-44, where the primers include an identifier tag sequence that is intermediate between the flanking target specific sequence and the 5' flanking tag sequence; col. 7, line 45 to col. 8, line 23),

with the first (P1) or second primers (P2) of the first primer pairs in each case differing in the intermediate segment i and in the second constituent segment (c2) or fourth constituent segment (c4) which is arranged in connection thereto, with each of the second (c2) or fourth constituent segments (c4) being specific for precisely one of the nucleic acids A (col. 4, lines 23-44, where the primers include an identifier tag sequence that is intermediate between the flanking target specific sequence and the 5' flanking tag sequence; col. 7, line 45 to col. 8, line 23, wherein the intermediate identifier sequence is specific for a target and are unique for each target and are incorporated into the primer sequence);

b) bringing the different nucleic acids A, or the nucleic acids A' which are complementary thereto, into contact with the first primer pairs in a solution and carrying out a first primer extension reaction in which the first primers (P1) are extended, under the first conditions, or the second primers (P2) are extended, under the second conditions, at least once and at least so far that the respective other primers (P2, P1) of the first primer pairs are able to bind specifically,

under the first or second conditions which are required for their specific hybridization, to in each case one first primer extension product which is formed in this connection (col. 4, lines 6-44, where the first and second primers are used in a primer extension reaction, producing fragment with set sequences at the respective ends),

e) bringing the second primer extension products into contact with the respective second primer pairs and carrying out a PCR, with in each case the intermediate segment i, or an intermediate segment i' which is complementary thereto, being amplified with the formation of third primer extension products (col. 18, line 60 to col. 19, line 12, where third and fourth primers specific for the tag sequence are used in PCR to amplify the intermediate identifying tag sequence),

f) providing in each case one immobilized probe (Pr) for each nucleic acid A to be detected, with the probe (Pr) being in each case able to hybridize specifically, under defined fourth conditions, with one of the intermediate segments i or one of the intermediate segments i' which are complementary thereto (col. 19, line 32 to col. 20, line 43, where the fragments are hybridized to an array of probes specific for the identifier sequence or 'intermediate' sequence, see especially col. 19, lines 33-41),

g) bringing the probes (Pr) into contact with the third primer extension products under the fourth conditions (col. 19, line 32 to col. 20, line 43, where the fragments are hybridized to an array of probes specific for the identifier sequence or 'intermediate' sequence, see especially col. 19, lines 33-41), and

h) detecting the third primer extension products which bind, or are bound, to the probes (Pr) (col. 19, line 32 to col. 20, line 43, where the fragments are hybridized to an array of probes specific for the identifier sequence or 'intermediate' sequence, see especially col. 19, lines 33-41).

With regard to claim 5, Wong teaches an embodiment of claim 1, wherein the sequences of the first constituent segment (cl) and third constituent segment (c3) are selected such that the third conditions can be so stringent that the second constituent segment (c2) does not significantly hybridize, under the third conditions, with the first segment of the one of the nucleic acids A and the fourth constituent segment (c4) does not significantly hybridize, under the third conditions, with the second segment of the nucleic acid A' which is complementary to the one of the nucleic acids A (col. 4, lines 45-60, where when the primer-tag-primer of Figure 1B is used in the method, primers complementary to the flanking sequences in the primer amplifies the identifier tag sequence incorporated into the amplified and extended fragments).

With regard to claim 6, Wong teaches an embodiment of claim 1, wherein the sequences and concentrations of the first (P1), second (P2), third (P3) and fourth primers (P4) are selected such that the specific annealing temperatures of the third primer (P3), which hybridizes with the sequence which is complementary to the first constituent segment (cl), and of the fourth primer (P4), which hybridizes with the sequence which is complementary to the third constituent segment (c3), are in each case at least 5°C higher than the in each case higher annealing temperatures of the second constituent segment (c2), which hybridizes with the first segment of one of the nucleic acids A, and of the fourth constituent segment (c4), which hybridizes with the second segment of the complementary nucleic acid A' (col. 4, lines 45-60, where when the primer-tag-primer of Figure 1B is used in the method, primers complementary to the flanking sequences in the primer amplifies the identifier tag sequence incorporated into the amplified and extended fragments).

With regard to claim 7, Wong teaches an embodiment of claim 1, wherein step e is carried out in the solution (col. 18, line 60 to col. 19, line 12, where third and fourth primers specific for the tag sequence are used in PCR to amplify the intermediate identifying tag sequence).

With regard to claim 8, Wong teaches an embodiment of claim 1, wherein at least steps a to e, in particular steps a to h, are carried out in a closed vessel which is not opened between the steps (col. 18, line 60 to col. 19, line 12, where third and fourth primers specific for the tag sequence are used in PCR to amplify the intermediate identifying tag sequence).

With regard to claim 15, Wong teaches an embodiment of claim 1, wherein a multiplicity of first primer pairs whose first primers (P1) exhibit an in each case identical or almost identical first constituent segment (c1) and/or whose second primers (P2) exhibit an in each case identical or almost identical third constituent segment (c3), and whose second constituent segment (c2) or fourth constituent segment (c4) is in each case specific for precisely one of the nucleic acids A, is added to the solution (col. 4, lines 45-60, where when the primer-tag-primer of Figure 1B is used in the method, primers complementary to the flanking sequences in the primer amplifies the identifier tag sequence incorporated into the amplified and extended fragments).

With regard to claim 17, Wong teaches an embodiment of claim 1, wherein the sequences of the intermediate segments i are selected such that neither they themselves, nor the intermediate segments i' which are complementary thereto, hybridize, in the method, with themselves or with the first (c1), second (c2), third (c3) or fourth constituent segments (c4) or their complementary sequences (col. 7, lines 45 to col. 8, line 4, where the identifier tag is

selected so that it is unique and does not comprise cross-hybridization with each other or with other components under stringent hybridization conditions).

With regard to claim 18, Wong teaches an embodiment of claim 1, wherein the sequences of the intermediate segments i are selected such that hybrids of the intermediate segments i with nucleic acids which were in each case completely complementary thereto would have melting temperatures which are essentially identical, lying, in particular, in a temperature range of 5°C (col. 7, lines 45 to col. 8, line 4, where the identifier tag or intermediate segments are selected so that hybrids have a melting temperature within a specific temperature range).

With regard to claim 19, Wong teaches an embodiment of claim 1, wherein, for specifically detecting one of the nucleic acids A in the presence of another nucleic acid which only differs from the one of the nucleic acids A in one first base which is contained in the one of the nucleic acids A, the sequences of the first (P1) or second primers (P2) are selected such that the respective base of the second (c2) or fourth constituent segment (c4), which base is complementary to the first base or to a second base, which is complementary thereto, of a complementary nucleic acid A', is located at the 3' end, or in the vicinity of the 3' end, of the in each case first (P1) or second primer (P2) (col. 11, lines 44-60).

With regard to claim 21, Wong teaches an embodiment of claim 1, wherein the respective sequences of the first (P1), second (P2), third (P3) and fourth primers (P4), and of the probe (Pr), are selected such that in each case the first, in each case the second, in each case the third and/or in each case the fourth conditions for detecting the different nucleic acids A are identical (col. 7, lines 45 to col. 8, line 4, where the identifier tag or intermediate segments are selected so that hybrids have a melting temperature within a specific temperature range).

Regarding claim 1, Wong does not explicitly teach the use of a pair of PCR primers for step a) and instead refers to the first step of the method as requiring at least one primer for the extension of the original sample sequences and while this teaching could encompass PCR amplification, this teaching is not explicit therefore also does not explicitly teach the components of step c) where the carrying out a second primer extension reaction in which the first primer extension products in each case serve as a template and the respective second (P2) or first primers (P1) are extended, under the first or second conditions which are required for their specific hybridization with the respective first primer extension products, with the formation of in each case one second primer extension product. Furthermore, regarding step d) of claim 1, while Wong teaches flanking sequences, the sequences are not explicitly taught as at either end of an amplification product.

With regard to claim 1, Heath teaches amplification of sample using tagged primers in a PCR reaction (Figure 1, where the primers are used in a first PCR using the first pair of primers and again in the second round of amplification using the universal flanking primers; p. 273-274, 'universal primer quantitative fluorescent multiplex PCR' heading) and thereby teaches c) carrying out a second primer extension reaction in which the first primer extension products in each case serve as a template and the respective second (P2) or first primers (P1) are extended, under the first or second conditions which are required for their specific hybridization with the respective first primer extension products, with the formation of in each case one second primer extension product (Figure 1, where the primers are used in a first PCR using the first pair of primers and again in the second round of amplification using the universal flanking primers; p. 273-274, 'universal primer quantitative fluorescent multiplex PCR' heading); and

d) providing in each case one second primer pair which in each case contains a third primer (P3) and a fourth primer (P4) and which is suitable for carrying out a PCR together with the respective second primer extension products, with the sequences of the third primer (P3) and fourth primer (P4) being in each case selected such that the third primer (P3) can in each case hybridize specifically, under defined third conditions, with a sequence which is complementary to the first constituent segment (cl), and be enzymatically extended, and the fourth primer (P4) can in each case hybridize specifically, under defined third conditions, with a sequence which is complementary to the third constituent segment (c3) and be enzymatically extended (Figure 1, where the primers used in a first PCR using the first pair of primers with a universal tag (black) and in the second round of amplification the universal flanking primers are extended (unfilled rectangles) which correspond to the third and fourth primer, P3 and P4, which are complementary to the first and third constituent segments, which correspond to the universal tag (black) in the first set of primers in Figure 1; p. 273-274, 'universal primer quantitative fluorescent multiplex PCR' heading).

With regard to claim 2, Heath teaches an embodiment of claim 1, wherein the first primer extension reaction and the second primer extension reaction are carried out as PCRs (Figure 1, where the primers are used in a first PCR using the first pair of primers and again in the second round of amplification using the universal flanking primers).

With regard to claim 4, Heath teaches an embodiment of claim 1, wherein the first primer extension reaction is carried out, under the first conditions, and/or the second primer extension reaction is carried out, under the second conditions, at most 10 times, preferably at most 5 times,

in particular at most 2 times (p. 274, where the first primer extension reaction is carried out for at most 10 times).

With regard to claim 9, Heath teaches an embodiment of claim 1, wherein the concentration, in the solution, of the first or second primer (P1, P2) containing the intermediate segment i is selected to be so low that this primer (P1, P2) does not significantly inhibit a hybridization of the probe (Pr) with the respective intermediate segment i, or the intermediate segment i' which is complementary thereto, of the third primer extension products in step g (p. 273-274, where the primers are added in differing concentrations, including from 3 pmol to 8 pmol.).

With regard to claim 12, Heath teaches an embodiment of claim 1, wherein the second primer pairs are added to the solution prior to the first primer extension reaction (Figure 1, where the primers are used in a first PCR using the first pair of primers and again in the second round of amplification using the universal flanking primers; p. 273-274, 'universal primer quantitative fluorescent multiplex PCR' heading).

With regard to claim 13, Heath teaches an embodiment of claim 1, wherein, in step e, in each case the third primer (P3) or the fourth primer (P4) is extended more frequently than is the respective other primer (P4, P3) of the respective second primer pairs (Figure 1, where the primers are used in a first PCR using the first pair of primers and again in the second round of amplification using the universal flanking primers).

With regard to claim 14, Heath teaches an embodiment of claim 1, wherein, in the second primer pair which is provided in step d, the third primer (P3) or the fourth primer (P4) is present

in excess as compared with the respective other primer (P4, P3) which is present therein (p. 273-274, where the primers are added in differing concentrations, including from 3 pmol to 8 pmol.).

With regard to claim 16, Heath teaches an embodiment of claim 1, wherein the sequences of the first (P1), second (P2), third (P3) and fourth primers (P4) are selected such that they do not form any primer dimers and/or do not hybridize with themselves or with each other in the method (p. 273-274, where the primers were designed as efficient for producing sequencing products).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the primer format of Wong, into the method of amplification taught by Heath to arrive at the claimed invention with a reasonable expectation for success. As taught by Heath, "the UPQFM-PCR is a rapid way of detecting major and minor rearrangements in any gene of interest. The method only requires small amounts of starting material which is then amplified, resolved by electrophoresis and quantified using fluorescence" (p. 277, col. 2). The two techniques share a 'universal' primer site and an intermediate region. The major differences lie in the means for detecting sequencing products. Heath detects the products using fluorescence detection in a thermal cycler, while Wong teaches detection through hybridization to a microarray. However, the methods are similar enough, regarding the inclusion of tagged primers and second round amplification using a tag specific primer, that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the universal tagged primer format taught by Wong in a PCR amplification technique, as taught by Heath with a reasonable expectation for success.

9. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280) as applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Moretti et al. (Biotechniques, 1998, vol. 25, no. 4, p. 716-722). Wong teaches a method that comprises amplification using tagged primers and hybridization of the amplification products to an identifying tag specific array (Abstract).

Wong in view of Heath teach the limitations of claims 1-2, 4-9, 12-19 and 21. However, neither teach amplification under hot start conditions. Moretti teaches amplification using a hot start polymerase (Abstract).

With regard to claim 3, Moretti teaches an embodiment of claim 1, wherein the first primer extension reaction and/or the second primer extension reaction and/or the PCR(s) is/are carried out under hot start conditions (materials and methods, p. 717-718).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Heath and Wong to incorporate the hot start amplification of Moretti to arrive at the claimed invention with a reasonable expectation for success. As taught by Moretti, "AmpliTaq Gold™ DNA polymerase is a thermostable enzyme that differs from AmpliTaq™ DNA polymerase by remaining inactive until exposed to a high temperature. It effectively simulates 'hot start' PCR in a fast, simple and practical fashion. The use of AmpliTaq Gold DNA polymerase can reduce or eliminate the generation of nonspecific PCR products that can result from mispriming'and primer oligomerization" (p. 716, col. 2 to p. 717, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Heath and Wong to incorporate the hot

start amplification of Moretti to arrive at the claimed invention with a reasonable expectation for success.

10. Claim 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280) as applied to claims 1-2, 4-9, 12-19 and 21 above. Wong teaches a method that comprises amplification using tagged primers and hybridization of the amplification products to an identifying tag specific array (Abstract).

With regard to claim 10, Heath teaches an embodiment of claim 1, wherein the concentration, in the solution, of the in each case first primer pair is set to be from 0.001 to 0.1 gmol/1 (p. 273-274, where the primers are added in differing concentrations, including from 3 pmol to 8 pmol.).

With regard to claim 11, Heath teaches an embodiment of claim 1, wherein the ratio of the concentrations of the in each case first primer pair to the in each case second primer pair is less than 1:10, preferably less than 1:100, particularly preferably less than 1:1000 (p. 273-274, where the primers are added in differing concentrations, including from 3 pmol to 8 pmol.).

While neither Heath nor Wong teach the specific concentration, an ordinary practitioner would have recognized that the results optimizable variables of time, product amount and concentration of primers could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the concentration chosen was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

11. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280) as applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Okimoto et al. (Biotechniques, 1996, vol. 21, no. 1, p. 20, 22, 24, 26). Wong teaches a method that comprises amplification using tagged primers and hybridization of the amplification products to an identifying tag specific array (Abstract).

Wong in view of Heath teach the limitations of claims 1-2, 4-9, 12-19 and 21. However, neither teach amplification using a primer comprising a mismatch sequence. Okimoto teaches a method for improved amplification of SNP alleles using internally mismatched primers (Abstract).

With regard to claim 20, Okimoto teaches an embodiment of claim 1, wherein the second (c2) or fourth constituent segments (c4) contain a base which is not complementary to a third base, which corresponds to it in its position, in the first segment of the one of the nucleic acids A or in the second segment of the nucleic acid A' (Table 1, where primers comprise mismatches to the wild-type sequence, see also Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of mismatched amplification to the teachings of

Heath and Wong to arrive at the claimed invention with a reasonable expectation for success. The methods taught by both Heath and Wong are directed to detection and sequencing of nucleic acids. As taught by Okimoto, "modification of PASA involves the use of internal primer mismatches to confer improved allele specificity. An additional mismatch (to all alleles) internal to the allele specific primer can improve specificity and also allow for the amplification of shorter PCR products" (p. 22, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have applied the method of mismatched amplification to the teachings of Heath and Wong to arrive at the claimed invention with a reasonable expectation for success.

12. Claims 22-26, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280) as applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Thorp et al. (WO 00/55366; September 2000). Wong teaches a method that comprises amplification using tagged primers and hybridization of the amplification products to an identifying tag specific array (Abstract).

With regard to claim 22, Wong teaches an embodiment of claim 1, wherein the probe (Pr) is in each case immobilized on an array or in its immediate vicinity (col. 19, line 32 to col. 20, line 43, where the fragments are hybridized to an array of probes specific for the identifier sequence or 'intermediate' sequence, see especially col. 19, lines 33-41).

With regard to claim 28, Wong teaches an embodiment of claim 1, wherein use is made of a multiplicity of different probes (Pr) which are complementary to the intermediate segments i

or to the intermediate segments i' which are complementary thereto, each of which probes is bound to, or in the immediate vicinity of, a separate array (col. 19, line 32 to col. 20, line 43, where the fragments are hybridized to an array of probes specific for the identifier sequence or 'intermediate' sequence, see especially col. 19, lines 33-41; , where a plurality of arrays are arranged on the surface).

With regard to claim 29, Wong teaches an embodiment of claim 1, wherein use is made of a multiplicity of arrays which are arranged on a surface, in particular an electrode chip, so as to be individually bonded or bondable (col. 19, line 32 to col. 20, line 43, where the fragments are hybridized to an array of probes specific for the identifier sequence or 'intermediate' sequence, see especially col. 19, lines 33-41; Figure 5, where a plurality of arrays are arranged on the surface).

Regarding claim 22, Wong does not teach the detection of a probe sequence immobilized on an electrode. Thorp teaches the detection of nucleic acid sequences using an electrode comprising a thin film on the conductive working surface, wherein a DNA probe is attached to a carboxylate group and in the presence of guanine containing moieties, an enhancement in oxidative current is observed (Abstract).

With regard to claim 22, 27, 28 and 29, Thorp teaches an embodiment of claim 1, wherein the probe (Pr) is in each case immobilized on an electrode (E) or in its immediate vicinity (Examples 3 and 4, where single stranded DNA is immobilized to an electrode and detected; see also Example 6, where guanine sequences were detected on the electrode and Examples 7 and 8 where immobilized probes are detected).

With regard to claim 23, Thorp teaches an embodiment of claim 1, wherein the detection in step h is effected by detecting a change in a fluorescence-optical property or a change, which is determined by the hybridization, in an electrical property at the electrode (E) (Example 6 and 8, where guanine sequences were detected on the electrode and in the presence of guanine a chance in conductivity is observed, see Abstract and p. 22-23, where the catalytic enhancement of oxidation current in the presence of a 20-mer G probe indicate that approximate 10 uC more charge or 10^-10 more moles of electrons are transferred when compared to oxidation of polymer alone).

With regard to claim 24, Thorp teaches an embodiment of claim 23, wherein a change in a redox property, in particular in association with the oxidation of guanine or adenine residues of the third primer extension products, in an impedance or in a conductivity is measured, as the change in the electrical property, using the electrode (E) (Example 6 and 8, where guanine sequences were detected on the electrode and in the presence of guanine a chance in conductivity is observed, see Abstract and p. 22-23, where the catalytic enhancement of oxidation current in the presence of a 20-mer G probe indicate that approximate 10 uC more charge or 10^-10 more moles of electrons are transferred when compared to oxidation of polymer alone).

With regard to claim 25, Thorp teaches an embodiment of claim 1, wherein the third primer (P3) and/or the fourth primer (P4) exhibits a label which can be detected, in particular, fluorescence-optically or electrically or electrochemically by means of the electrode (E) and which is preferably redox-active (Example 6 and 8, where guanine sequences were detected on the electrode and in the presence of guanine a chance in conductivity is observed, see Abstract and p. 22-23, where the catalytic enhancement of oxidation current in the presence of a 20-mer G

probe indicate that approximate 10 uC more charge or 10^-10 more moles of electrons are transferred when compared to oxidation of polymer alone).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the thin film electrode teachings of Thorp to the method of sequence analysis taught by Heath and Wong to arrive at the claimed invention with a reasonable expectation for success. As taught by Thorp, "the electrode of the invention is useful for the electrochemical detection of aqueous GMP, poly G and surface immobilized nucleic acids containing a preselected base" (p. 7-8). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the thin film electrode teachings of Thorp to the method of sequence analysis taught by Heath and Wong to arrive at the claimed invention with a reasonable expectation for success.

13. Claims 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280) and Thorp et al. (WO 00/55366; September 2000) as applied to claims 22-26, 28 and 29 above, and further in view of Jenison et al. (Biosensors and Bioelectronics 2001, vol. 16, p. 757-763). Wong teaches a method that comprises amplification using tagged primers and hybridization of the amplification products to an identifying tag specific array (Abstract). Wong in view of Heath and Thorp teach all of the limitation of claims 22-26, 28 and 29 as recited above. However, none of these references teach that the label comprises an affinity molecule and that it is detected using a counter molecule. Jenison teaches a thin film biosensor

wherein the sample is labeled with biotin and detected using a change in color through horseradish peroxidase (Abstract).

With regard to claim 26, Jenison teaches an embodiment of claim 25, wherein the label exhibits a specific affinity molecule, an osmium complex, a nanogold particle, a cysteine, ferrocenyl, daunomycin, benzoquinone, naphthoquinone, anthraquinone or p aminophenol group, a dye, in particular indophenol, thiazine or phenazine, or a fluorescent dye, in particular 6-FAM, HEX, TET, Cy3, Cy5, IILDyeTM700, IRDyeTM800, Biodipy, fluorescein, Joe, Rox, TAIVIRA or Texas Red (Figure 1, where the detector sequence is labeled with biotin).

With regard to claim 27, Jenison teaches an embodiment of claim 25, wherein the label is an affinity molecule and it is detected using a counter molecule which specifically binds the affinity molecule, with the counter molecule being conjugated with an enzyme which can convert a substrate such that the reaction product can be specifically detected electrochemically or optically (Figure 1, where the detector sequence is labeled with biotin and detected using an anti-biotin antibody labeled with horseradish peroxidase).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Heath, Wong and Thorp to include the means of detection taught by Jenison to arrive at the claimed invention with a reasonable expectation for success. As taught by Jenison, "rapid, sensitive assays for nucleic acid amplification products have utility for the identification of bacterial or viral infections. We have developed a nucleic acid hybridization assay utilizing thin film technology that permits visual detection of hybrids. The silicon-based biosensor detects the presence of target sequences by enzymatically transducing the formation of nucleic acid hybrids into molecular thin films. These

films alter the interference pattern of light on the biosensor surface" (Abstract). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Heath, Wong and Thorp to include the means of detection taught by Jenison to arrive at the claimed invention with a reasonable expectation for success.

14. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (US Patent 5,935,793; August 1999) in view of Heath et al. (Journal of Medical Genetics, 2000, 37: 272-280) as applied to claims 1-2, 4-9, 12-19 and 21 above, and further in view of Eberwine et al. (PNAS, 1992, vol. 89, p. 3010-3014). Wong teaches a method of sequencing using tagged primers that are hybridized to an array to identify the sequence (Abstract).

Wong in view of Heath teach the limitations of claims 1-2, 4-9, 12-19 and 21. However, neither teach detection of RNA using transcription into DNA. Eberwine teaches the detection of RNA samples through transcription of the RNA into DNA (Abstract).

With regard to claim 30, Eberwine teaches an embodiment of claim 1, wherein an RNA is detected indirectly by transcribing it into a DNA and then detecting the DNA as nucleic acid A (Figure 2, where RNA is transcribed into DNA and see p. 3011, 'materials and methods' heading).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Heath and Wong to include the ability to detect RNA samples using a DNA platform following transcription of the RNA into DNA as taught by Eberwine to arrive at the claimed invention with a reasonable expectation for success. As taught by Eberwine, "the first step is the synthesis of an oligo(dT) primer that is extended at

the 5' end with a T7 RNA polymerase promoter. This oligonucleotide can be used to prime the poly(A)+ mRNA population for cDNA synthesis" (p. 3010, col. 1). The ability to detect not only DNA sequences but also to detect RNA sequences as taught by Eberwine provides flexibility to the method taught by Heath and Wong. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have modified the teachings of Heath and Wong to include the ability to detect RNA samples using a DNA platform following transcription of the RNA into DNA as taught by Eberwine to arrive at the claimed invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments filed October 1, 2009 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claims as obvious over Wong in view of Heath. While Applicant's arguments have been carefully considered, they are not persuasive. Applicant argues "apart from the primer extension reaction, the methods of Heath and Wong do not share any other common feature" and "serve different puproses and comprise different method steps" (p. 3 of remarks). Applicant argues that "the 'tag' sequence of Heath is a stretch of 6 nucleotides for DNA sequencing and "is actually a binding site for a DNA sequencing primer that is identical in the different PCR products" and "is in fact another universal primer sie to which a sequencing primer can bind". Applicant concludes "the teaching of Heath does not disclose a true unique "tag" sequence for identifcation purposes". Applicant also argues "the use of a second primer as taught by Heath in the method of Wong would not be feasible" (p. 4 of remarks).

Next, Applicant argues at length why a second primer would not be obvious or compatible with the teachings of Wong (see p. 5-6 of remarks). Applicant also argues "the primer format taught by Wong cannot be used in a method as taught by Heath". Applicant argues that "the general structure of the primers of Wong is depicted in Figures 1A and 1B" and "the primers share a universal sequence at their 3' end that is referred to as 26 in Fig. 1A and 44 in Fig. 1B... and a unique tag sequence that is designated 22 in Fig. 1A and 42 in Fig. 1B". Applicant argues "the primers depicted in Fig. 1A and 1B are extended in the method taught by Wong via the universal binding sites at their 3' ends" and "it is evident that such a primer would simply not be suitable for use in the method of Heath" because "the method of Heath does not work with a universal primer site in the target sequence.. the 3' ends of the primers used by Heath are target-specific primers" (p. 7 of remarks).

As noted above, Applicant's arguments have been considered, but are not persuasive. Applicant is both misinterpreting the rejections of record and reading the cited passages of the references given an extremely narrow and literal interpretation of the terms "tag" and "universal" in a manner which is not supported or asserted by the rejections. Therefore, for at least this reason, Applicant's arguments are wholly unpersuasive.

Again, as noted in the prior office action, as noted in the prior rejection, it would have been prima facie obvious to incorporate the primer format taught by Wong in a method of PCR amplification, as taught by Heath. Therefore, while applicant disagrees with the combination, Applicant's arguments regarding the lack of obviousness of incorporating a second primer into the method of Wong are also not persuasive.

Next, it appears it would be helpful to summarize the rejection in the context of Applicant's arguments because it appears that Applicant is not understanding the Examiner's position regarding the elements of the claimed invention. Contrary to Applicant's arguments, the primer format of Wong is, in fact amenable to, and can be used in the method taught by Heath. Regarding the Wong reference, Applicant is apparently disregarding the basis for the rejection set forth clearly and distinctly above. The rejection of the primer elements refers specifically to Figure 1B and element 46, which corresponds to a 5' "universal" flanking sequence, element 42, which is the connecting intermediate "identifying" tag and element 44, which corresponds to target sequence. While Wong refers to the 44 sequence as "universal" because it corresponds to a primer binding site, the sequence is not universal in the context of the instant invention. Instead, it actually corresponds to the binding site of the primer on the plasmid target and varies depending on the plasmid target sequence. Therefore it is a target specific sequence and does not correspond to the "universal" flanking region referred to specifically in the rejection. To make it as explicitly clear as possible, referring specifically to Figure 1B, segment 46 corresponds to the "flanking" C1/C3 region of the primers of Applicant's claims, 44 corresponds to C4/C2 region of the primers of Applicant's claims, which hybridizes to the target nucleic acid. Finally, element 42, and NOT element 46 corresponds to the differing and distinct intermediate (i) segment of the claims, which provides identification for each target sequence. Therefore, in light of this clarification is should hopefully be clear that Applicant's arguments regarding the "tag" element of both Heath and Wong are entirely misplaced and therefore unpersuasive.

For example, Applicant argues regarding Wong that the primer of Figure 1B would not function in a method of PCR as taught by Heath because the primer "is extended starting from

the 3' end" "via the universal binding sites at their 3' ends". While it is true that Wong uses the phrase "universal" in connection with the primer binding sequence 44, it is again emphasized that the term universal does not have the same meaning as in the context of Applicant's claims. At col. 21, Wong also states "each tag-primer includes at its 3' end, a first 'universal' primer region for hybridizing to the plasmid DNA immediately upstream of the sample insert". Regarding this sequence, Wong also states that "reactions may be conducted in parallel for a large number of different plasmid samples...thus, a sequencing fragment mixture prepared from k sample fragments will contain a plurality of sequencing fragments containing different primer-tag-primer sequences" (see Table 1). Therefore, while the primer sequence 44 may be "universal" for a specific plasmid sequence to amplify different inserts, it is clear from the passage of Wong that the primer site is also different depending on the plasmid target the primer is binding to and therefore 44 is actually target specific in this context.

Next, while Applicant's arguments against Heath are noted, Applicant's arguments are not persuasive. Applicant appears to be arguing that the 6 basepair "tag" of Heath does not correspond to the identifying tag of the claimed invention. A careful review of the rejection should make clear that the rejection in no way suggests that the "tag" of Heath corresponds to the intermediate identification "tag" of the instant invention. Instead, it is clear from the rejection that it is the "universal" 5' most tag of the universal primer is relied upon in the rejection, and is therefore clearly and necessarily not unique to each target, otherwise it would not be universal. Instead, the "identifying tag" element of the intermediate (i) region of the claimed primers is rendered obvious as taught by Wong, not by Heath. As noted by Applicant, and as presented in the rejection, the "universal" or common sequence of the primers taught by Heath render obvious

the P3/P4 primers claimed by Applicant, because these common or universal sequences or "tags" taught by Heath serve the exact same purpose as Applicant's claimed primer elements. In other words, as taught by Wong and by Heath, a common or universal sequence is incorporated onto the 5' end of a primer in a first round of primer extension, and then in a second round of amplification, this 5' common/universal sequence is bound by a common "P3/P4" primer pair directed to the common/universal sequence. Therefore, each of the elements of the claimed primers and primer extension reactions are rendered obvious by a combination of Wong and Heath.

Finally, it is noted Wong also teaches the step of detecting the target specific "identifying tag", which corresponds to 42 of Fig. 1B using an array of probes that are directed to the intermediate sequence of 42. Therefore, Applicant's arguments are not persuasive and the rejection is maintained.

Conclusion

No claims are allowed. All claims stand rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Examiner, Art Unit 1637

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/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637